CLAIMS

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1. A method of preparing a somatic cell for nuclear transfer comprising modifying the genetic material of the somatic cell by a genetic targeting event.

2. A method as claimed in claim 1, wherein the genetic targeting event is mediated by homologous recombination.

3. A method, as claimed in claim 1 or claim 2, wherein the modification is inactivation, removal or modification of a gene; upregulation of a gene, gene replacement or transgene placement.

4. A method as claimed in any one of claims 1 to 3, wherein the genetic targeting event results in a gene targeted cell clone:randomly targeted cell clone ratio of equal to or greater than 1:100.

5. A method as claimed in any one of claims 1 to 4 wherein the gene targeting event is carried out at a locus abundantly expressed in the host somatic cell.

6. A method as claimed in any one of claims 1 to 5 wherein a structural gene is placed adjacent to an endogenous promoter.

7. A method as claimed in claim 6 wherein the endogenous promoter is that of a collagen gene.

8. A method as claimed in claim 6 wherein the endogenous promoter is that of a milk protein gene.

9. A method as claimed in claim 6 wherein the endogenous promoter directs abundant expression in fibroblast cells.

10. A method as claimed in claim 6 wherein the endogenous promoter directs abundant expression in endothelial cells.

11. A method as claimed in any one of claims 1 to 10 wherein the genetic targeting event is mediated by lipofection.

12. A method as claimed in any one of claims 1 to 11 wherein the genetic targeting event involves the use of a gene targeting vector which vector comprises a long region of homology to the target locus.

13. A method as claimed in any one of claims 1 to 12 wherein the genetic targeting event involves the use of a gene targeting vector which is in a circular form.

14. A method as claimed in any one of claims 1 to 13 wherein the genetic targeting event includes the artificial induction of gene expression or the induction of chromatin changes in the cell.

15. A method as claimed in any one of claims 1 to 14 wherein the genetic targeting event is facilitated by an agent which inhibits histone deacetylation or by expression in the cell of a factor which stimulates transcription at the target locus.

16. A method as claimed in any one of claims 1 to 15, wherein the somatic cell is a primary somatic cell.

17. A method as claimed in any one of claims 1 to 16, wherein the somatic cell is an epithelial cell, or a fibroblast cell, or an endothelial cell, or a muscle cell.

18. A method of nuclear transfer comprising a method as claimed in any one of claims 1 to 17 and a method comprising transfer of the genetic material from the somatic cell to a recipient cell.

19. A method, as claimed in claim 18, wherein the transfer of the genetic material from the somatic cell, to a recipient cell, provides an animal embryo.

20. A method, as claimed in claim 18 or claim 19 further comprising the production of a totipotent or pluripotent cloned cell population.

21. A transgenic cell, suitable for nuclear transfer obtainable by a method as claimed in any one of claims 1 to 17.

22. A transgenic embryo or a transgenic fetus obtainable by a method as claimed in claim 19.

23. A method for preparing a transgenic animal, comprising causing an animal to develop to term from the embryo as claimed in claim 22 and optionally breeding from the animal.

24. A transgenic animal obtainable by the method as claimed in claim 23.

25. A transgenic animal as claimed in claim 24 which is a sheep, cow, bull, goat, pig, horse, camel, rabbit or rodent.

26. A transgenic animal which is bred from an animal as claimed in claim 24 or claim 25.

27. A method for obtaining a clonal pluripotent or totipotent cell population comprising culturing a cell line from a transgenic embryo or a transgenic fetus as claimed in claim 22.

28. A clonal pluripotent or totipotent cell population obtainable according to a method as claimed in claim 27.

29. A method for modifying the genetic material of a somatic cell while maintaining the totipotency of the cell, the method comprising a genetic targeting event.

30. A method as claimed in claim 29, wherein the genetic targeting event is mediated by homologous recombination.

31. A method as claimed in claim 29 or claim 30 wherein the modification is inactivation, removal or modification of a gene, upregulation of a gene, gene replacement or transgene placement.

32. A method as claimed in any one of claims 29 to 31, wherein the genetic targeting event results in a gene targeted cell clone:randomly targeted cell clone ratio of equal to or greater than 1:100.

33. A method as claimed in any one of claims 29 to 32 wherein the gene targeting event is carried out at a locus abundantly expressed in the host somatic cell.

34. A method as claimed in any one of claims 29 to 33 wherein a structural gene is placed adjacent to an endogenous promoter.

35. A method as claimed in claim 34 wherein the endogenous promoter is that of a collagen gene.

36. A method as claimed in claim 34 wherein the endogenous promoter is that of a milk protein gene.

37. A method as claimed in claim 34 wherein the endogenous promoter directs abundant expression in fibroblast cells.

38. A method as claimed in claim 34 wherein the endogenous promoter directs abundant expression in endothelial cells.

39. A method as claimed in any one of claims 29 to 38 wherein the genetic targeting event is mediated by lipofection.

40. A method as claimed in any one of claims 29 to 39 wherein the genetic targeting event involves the use of a gene targeting vector which vector comprises a long region of homology to the target locus.

41. A method as claimed in any one of claims 29 to 40 wherein the genetic targeting event involves the use of a gene targeting vectory which is in a circular form.

42. A method as claimed in any one of claims 29 to 41 wherein the somatic cell is a primary somatic cell.

43. A method as claimed in any one of claims 29 to 42, wherein the genetic targeting event includes the artificial induction of gene expression or the induction of chromatin changes in the cell.

44. A method as claimed in any one of claims 29 to 43, wherein the genetic targeting event is facilitated by an agent which inhibits histone deacetylation or by expression in the cell of a factor which stimulates transcription at the target locus.

45. A method as claimed in any one of claims 29 to 44, in combination with a method comprising the transfer of the genetic material from the somatic cell to a recipient cell.

46. The use of artificial induction of gene expression or induction of chromatin changes in the genetic targeting of a cell.

47. The use of a gene targeting vector which is in a circular form in the modification of the genetic material of a cell by a gene targeting event.

48. The use, as claimed in claim 46 or claim 47, wherein the cell is somatic or non-somatic.

49. The use, as claimed in any one of claims 46 to 48, wherein the genetic targeting is facilitated by an agent which inhibits histone deacetylation or by expression in the cell of a factor which stimulates transcription at the target locus.

50. The use, as claimed in any one of claims 46 to 49, in combination with the nuclear transfer of the genetic material of the cell into a suitable recipient cell.

51. The use of an animal, which has been obtained from a cell following a genetic targeting event, to test for genetic changes due to the location of the genetic targeting.

52. The use, as claimed in claim 51, wherein the cell is a somatic cell and the production of the animal includes nuclear transfer.

53. The use, as claimed in claim 51 or claim 52, wherein the somatic cell is a primary somatic cell.

54. The use, as claimed in claim 52 or claim 53, wherein the cell is a fibroblast.

55. The use, as claimed in any one of claims 51 to 54, wherein the gene targeting event is as described in any one of claims 2 to 13.

56. A method for validating a locus for targeted gene therapy comprising:

- obtaining cells of a chosen type;
- introducing a desired genetic change at a selected locus;
- growing a clonal population of the targeted cells; and
- demonstrating through the production of an animal that the genetic changes are acceptable.

57. A method, as claimed in claim 56, wherein the production of the animal involves nuclear transfer.

58. A method, as claimed in claim 57, wherein the cell is a fibroblast.

59. A method as claimed in claim 56, wherein the cell is an embryonic stem (ES) cell or an embryonic germ (EG) cell.

60. A method as claimed in claim 59, wherein the animal is a chimeric animal.

61. A validated locus, obtainable by the method of any one of claims 56 to 60.